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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/626,943

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Joseph T. Rubino

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HOWSON & HOWSON LLP / WYETH

501 OFFICE CENTER DRIVE

SUITE 210

FORT WASHINGTON, PA 19034

EXAMINER

POLANSKY, GREGG

ART UNIT

PAPER NUMBER

1614

NOTIFICATION DATE

DELIVERY MODE

11/13/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@howsonandhowson.com

Office Action Summary	Application No. 10/626,943	Applicant(s) RUBINO ET AL.	
	Examiner GREGG POLANSKY	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-16, 18 and 31-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-16, 18 and 31-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/16/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 9/16/2009 has been entered.
2. Applicants' Information Disclosure Statement, filed 9/16/2009, is acknowledged and has been reviewed. Non-English language documents have been reviewed to the extent of: (a) any provided translations or the corresponding English language International or U.S. Applications, and of (b) discussion of relevant sections of the documents by Applicants' in their Remarks.
3. The Advisory Action mailed 6/08/2009 inadvertently indicated the status of Claims 38 and 39 as Allowed and Claims 13-16, 18 and 31-37 as Rejected (see Advisory Action item 7). The text of item 5 indicated Applicants' amendments had overcome the rejection of Claim 38 and 39 under 35 USC 112 2nd paragraph. This is correct. However, the rejection under 35 USC 103(a) was maintained and the rejected claims listed in item 7 should have been Claims 12-16, 18 and 31-39 (i.e., includes Claims 38 and 39).
4. Claims 13-16, 18, and 31-39 are pending and presently under consideration.

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5. Applicants have provided copies of 2 oppositions filed in the corresponding European Patent No. 1 553 940. Applicants have also provided copies of the documents cited in the 2 oppositions. All provided documents have been considered with regard to the instant application. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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8. Claims 13-16, 18, and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skotnicki et al. (U.S. Patent No. 5,362,718), in view of Waranis et al. (U.S. Patent No. 5,516,770) and Haeberlin et al. (UK Patent Application Publication GB 2327611). Maintained from previous Office action.

Skotnicki et al. teach hydroxyester derivatives of rapamycin, including the instantly claimed CCI-779 (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid), and that these derivatives are useful as immunosuppressive, anti-inflammatory, antifungal, antiproliferative, and antitumor agents. See column 1, 1st paragraph and last paragraph, and column 12, "EXAMPLE 9". The reference suggests the rapamycin derivatives can be formulated with suitable carriers, including alcoholic solvents, and excipients for *inter alia* oral or parenteral administration. See columns 7 and 8.

Skotnicki et al. do not teach the formulations of CCI-779 recited by the instant claims.

Waranis et al. teach an injectable rapamycin solution comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water (see Examples 1-3), yielding an injectable formulation concentration of rapamycin of 0.2 mg/ml to 4 mg/ml (see column 2, lines 44-47), with 0.07-9.5% polysorbate 80 and 12-87% glycols (see column 3, lines 29-54). These concentrations are within the concentration ranges specified in the claims of the instant application.

Waranis et al. do not teach use of an antioxidant. Waranis et al. teach formulations of rapamycins, but not CCI-779 specifically. Waranis et al do not teach a formulation comprising ethanol (recited by instant Claims 32 and 38) or vitamin E (d,l- α -tocopherol) (recited by instant Claims 33, 34, 36, 38 and 39).

Haeberlin et al. teach the use of various carboxylic acids to stabilize (i.e., preserve) oral and parenteral formulations of macrolides, preferably a rapamycin. The reference teaches that macrolides [note: this would include CCI-779] are unstable upon storage, undergoing a variety of different degradation reactions and an acidic environment inhibits the degradation. See page 3. The preferred acids include malonic acid, oxalic acid, citric acid, and lactic acid (see page 4, lines 15-22). Haeberlin et al. teach a 0.05% to 5% acid concentration range and further disclose that the preferred amount of acid may be determined by routine experimentation. Haeberlin et al. give as an example, a formulation of a rapamycin with absolute (dehydrated) ethanol, Cremophor[®] EL (a surfactant), and citric acid. They present other examples of rapamycin formulations which include the use of 1,2 propylene glycol as a solvent and d,l- α -tocopherol (vitamin E) as an antioxidant. See pages 5-7.

With respect to claimed concentration ranges in the instant compositions, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11).

It would have been obvious to one of ordinary skill in the art at the time of the invention, who was motivated to produce parenteral formulations of rapamycins,

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including CCI-779, to combine the teachings of Skotnicki et al., which discloses hydroxyester rapamycin derivatives and formulations thereof, with those of Waranis et al. and Haeberlin et al., which teach rapamycin formulations. Waranis et al. teach the concentrations of the solvents (e.g., propylene glycol, absolute ethanol, and polyethylene glycol 400), rapamycin, and a specific surfactant (polysorbate 80) for a parenteral rapamycin formulation. Haeberlin et al. teach the instability of rapamycins and the need to use citric acid and d,l- α -tocopherol as a stabilizer in a rapamycin parenteral formulation. This would have motivated one to include citric acid/d,l- α -tocopherol in the formulations taught by the other two references. Since Skotnicki et al. do not teach specific formulations, one would have been motivated to find art teaching specific formulations of rapamycins, including CCI-779, such as is taught by Waranis et al. and Haeberlin et al. One would have been motivated to perfect a parental formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g., oral), leading to more accurate and reproducible doses of the agent.

Applicants have previously presented arguments and amended claims (filed 5/14/2009) in response to the Office action mailed 3/18/2009. Applicants' arguments were found to be non-persuasive, as discussed in the Office Advisor Action, mailed 6/08/2009.

The documents and IDS submitted by Applicants (filed 9/16/2009) have been fully considered. Applicants have not pointed to any showing by these documents that overcomes the rejection of record.

Conclusion

9. Claims 13-16, 18, and 31-39 are rejected.
10. No claims are allowed.
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

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/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614